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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,118	12/11/2003	Sarah S. Bacus	CST-213	4570

7590 04/02/2009

James Gregory Cullem, Esq.
Intellectual Property Counsel
CELL SIGNALING TECHNOLOGY, INC.
3 Trask Lane
Danvers, MA 01923

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
04/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,118	BACUS ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-113* is/are pending in the application.

4a) Of the above claim(s) *86,90-98,102,104 and 108-110* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,85,87-89,99-101,103,105-107 and 111-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed February 4, 2009 in response to the Office Action of Sept 4, 2008 is acknowledged. Applicant elected with traverse Group I, claims 84-107 and 111-113). Applicants elected with traverse the species of assaying phosphorylation of an S6 ribosomal polypeptide and expression of an IGFR.

2. Applicants argue that the examination of Groups I and II would not be undue burden because of the close-interrelatedness between the claimed methods and kits. Applicants argue that one of ordinary skill in the art would realize upon reading the specification that the most logical use of the kits of the Group II is to perform the methods of the Group I invention (p. 9).

The arguments have been considered but are not found persuasive because as stated in the restriction requirement: The inventions can be shown to be distinct if the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the antibodies of Group II can be used for affinity chromatography or to produce anti-idiotypic antibodies. Further, there is undue search burden on the Examiner because (a) the inventions have acquired a separate status in the art in view of their different classification; (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); (d) the prior art applicable to one invention is not likely be applicable to another invention;

and (e) the inventions raise different non-prior art issues under 35 U.S.C. 112, first paragraph. For these reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Applicants argue that there are not an unreasonable number of species in the Group I invention claims and although different reagents are used, there are only two different criteria for success. Applicants argue that for the expression assays, either the indicated polypeptide is expressed or it is not and for the phosphorylation assay, either the indicated polypeptide is phosphorylated or it is not (p. 10).

The arguments have been considered but are not found persuasive because as stated in the restriction requirement: The species are independent or distinct because each method step requires distinct reagents, different response variables, and criteria for success, and claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record. The criteria for success are much more extensive than Applicants state, requiring an undue search burden on Examiner. The method of Group I requires identifying a HER-2 over-expressing mammalian tumor that is likely to respond to a HER-2 directed therapy based on any combination of different protein species' phosphorylation patterns or expression patterns, and each combinations of proteins and various patterns would require separate searches and each raise different non-prior art issues under 35 U.S.C. 112, first paragraph. For these

reasons, the restriction requirement is deemed to be proper and is therefore made FINAL.

4. Claims 84-113 are pending. Claims 108-110 are withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 86, 90-98, 102, 104 are withdrawn as being drawn to non-elected species. Claims 84, 85, 87-89, 99-101, 103, 105-107, 111-113 are currently being examined as drawn to the elected species of assaying phosphorylation of an S6 ribosomal polypeptide and expression of an IGFR.

Specification

5. The specification is objected to for the following reason: The specification on page 1 should be amended to reflect the most current priority status of the present application, including proper reference to applications that have been issued or abandoned. For example Application 10/408,520 is now abandoned. See specification amendment filed July 19, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 87 and 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 87 and 103 are indefinite because they recite the phrase **"specific for"** to indicate the claimed antibody's function for an epitope. This renders the claim indefinite because it is unclear what function the antibody had "specific for" the epitope. Given the above reasons, the metes and bounds of the claims cannot be determined. Amendment of the claims to recite "that binds to" would obviate the rejection.

7. Claims 100 and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite in the use of the term **"rhuMAb Her2"** and it is unclear if rhuMAb Her2 and HERCEPTIN® are one in the same given the specification places "HERCEPTIN®" in parenthesis after stating the term "rhuMAb Her2" (p. 9, line 11). For example, HERCEPTIN® is monospecific to an epitope on HER2 and manufactured by Genentech, whereas "rhuMAb Her2" may describe a genus of monospecific antibodies that bind to differing epitopes on HER2. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 84, 85, 87-89, 99-101, 103, 105-107, 111-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for identifying a HER-2 over-expressing mammalian tumor that is likely to respond to a HER-2 directed therapy, the method comprising the steps of:

(i) assaying a sample obtained from the mammalian tumor to detect a pattern of:

(a) phosphorylation of an S6 ribosomal polypeptide;

(b) expression of an IGFR (Insulin-like Growth Factor Receptor) polypeptide; and

(ii) comparing said pattern to a pattern detected in a sample obtained from a non- tumor tissue or cell sample, wherein a change in the detected pattern identifies said mammalian tumor as likely to respond to a HER-2 directed therapy (claim 84, 87, 89, 101, 103, 105, 112), the method of claim 84, wherein the detected pattern is increased phosphorylation of S6 ribosomal polypeptide, accompanied by decreased expression of IGFR polypeptide in the mammalian tumor as compared to said non-tumor tissue or cell sample, wherein said pattern identifies said tumor as likely to respond to a HER-2 directed therapy (claim 85), wherein said mammalian tumor is a breast tumor (claims 88, 107), the method of claim 89, wherein the detected pattern of expression and phosphorylation is determined subsequent to contacting the sample obtained from the mammalian tumor with a HER-2 directed therapy (claim 99), wherein the HER-2 directed therapy comprises rhuMAb HER-2 (claims 100, 111), wherein the mammalian tumor is identified as overexpressing HER-2 (claims 106, 113).

The specification discloses that utilizing a panel of phospho-specific antibodies to profile signal transduction pathway activation in cellular samples from a plurality of patients having a particular disease, coupled with determining correlations among

activation statuses of multiple proteins in a pathway and a given outcome (e.g. disease progression, therapeutic responsiveness, survival, etc.) enables the identification of the most relevant and statistically-significant biomarkers of the given outcome (p. 7, lines 24-26 to p. 8, lines 1-5). The specification discloses examples of detecting the presence or absence of IGFR and presence or absence of phosphorylated S6 as correlated to response to HERCEPTIN® therapy only in breast cancer patients overexpressing HER2 (Tables 1-6). The specification demonstrates that the presence or absence of S6 phosphorylation alone was not predictably correlated to a response to HERCEPTIN® therapy (p. 27, lines 28-31; Table 4). However, the specification discloses that the presence or absence of IGFR expression predicted HERCEPTIN® therapy response, wherein IGFR negative patients had higher response rates to HERCEPTIN® therapy than IGFR positive patients (Table 2). Further, the specification discloses that 67% of patients with combined IGFR negative and phosphorylated S6 positive breast cancer responded to HERCEPTIN® therapy and only 26% of patients with combined IGFR negative and phosphorylated S6 negative samples responded to HERCEPTIN® therapy (Table 5).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide any examples or guidance for a method for identifying **any HER2-overexpressing mammalian tumor** that is likely to respond to **any HER-2 directed therapy** comprising determining **any changes in pattern of S6 phosphorylation and IGFR expression between a sample obtained from the mammalian tumor and any sample obtained from any non-tumor tissue**

or cell sample. Although some dependent claims may further limit some variables (in bold) of the independent claims, they do not limit all of them. The specification provides only a nexus between HER-2 overexpressing breast tumors that are IGFR expression negative and positive for S6 phosphorylation and the increased likelihood of response to HERCEPTIN® therapy. The specification provides neither guidance on nor exemplification of how to predictably correlate any detected change in pattern in IGFR expression and S6 phosphorylation to any response to any HER-2 directed therapy for any cancer. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders and the predictable correlation between biomarkers and treatment outcome. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with

subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Given the teaching of the art, without a validated nexus provided between specific changes in phosphorylation or expression patterns for S6 and IGFR and the outcome of a specific treatment for a specific disease, one of skill in the art could not predictably use the claimed changes in phosphorylation or expression patterns for S6 and IGFR to identify treatment outcome to any HER-2 directed therapy for any HER-2 overexpressing cancer.

Similarly, one cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide guidance or examples for predictably identifying treatment outcome to HERCEPTIN® therapy based on **any phosphorylation of any S6 ribosomal polypeptide** other than for phosphorylation of SEQ ID NO:2 at residue 235. The claims as currently constituted are broadly drawn to assaying (any) phosphorylation of an (any) S6 ribosomal polypeptide. The art teaches that S6 ribosomal polypeptide (rpS6) comprises numerous phosphorylation sites in addition to Serine 235 and is found in many different unrelated species (see Ruvinsky et al ,Trends in Biochemical Sciences, 2006, 31:342-348, particularly p. 344, col. 1-2; Figure 3). Given the teaching in the art (Tockman et al

above), without a nexus provided between biomarker and subsequent treatment outcome, one of skill in the art could not predictably use any phosphorylation site on any S6 ribosomal polypeptide, other than serine 235 of SEQ ID NO:2, to identify a mammalian tumor likely to respond to HERCEPTIN® therapy without undue experimentation.

Similarly again, one cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide guidance or examples for predictably identifying treatment outcome to HERCEPTIN® therapy based on **any IGFR** polypeptide, and it does not appear the specification distinguishes which IGFR is detected. The art teaches there are at least two IGFR's, IGF-IR and IGF-IIR, both found in many unrelated species (see iHOP, p. 1-2). In related art, Lu et al (J National Cancer Institute, 2001, 93:1852-1857) teach *in vitro* Her-2 overexpressing breast cancer cell lines with inhibited or low insulin growth factor-1 receptor (IGF-IR or IGF-1R) expression are more susceptible to trastuzumab (HERCEPTIN®) than cells with IGF-IR expression (abstract). However, Köstler et al (J Cancer Research Clinical Oncology, 2006, 132:9-18) contradict this teaching for an *in vivo* study that measured IGF-1R status in HER-2 overexpressing breast tumors and determined that response to trastuzumab therapy was independent of IGF-1R expression, meaning IGF-1R did not predict therapeutic response for patients with HER-2 overexpressing breast tumors (abstract). The study done by Köstler et al teaches the unpredictability of using IGF-1R expression alone to determine patient response to trastuzumab. A search of relevant art does not appear to teach a relationship between IGF-IIR expression and response to

trastuzumab therapy. Given the teaching in the art (Tockman et al above), without a nexus provided between biomarker and subsequent treatment outcome, one of skill in the art could not predictably use any IGFR polypeptide expression to identify a mammalian tumor likely to respond to HERCEPTIN® therapy without undue experimentation.

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide **any comparison** of phosphorylation or expression patterns for S6 and IGFR in the HER-2 overexpressing breast tumor samples **to patterns found in any non-tumor tissue or cell sample**. The specification discloses only the detection of the *presence or absence* of IGFR expression or S6 phosphorylation and indicates such as "positive" or "negative" in Tables 2-7 of the Examples. No changes in detected patterns of IGFR expression or S6 phosphorylation as compared to any controls are measured and used to determine response to HERCEPTIN® therapy. The instant claims require a comparison between a HER-2 overexpressing tumor and non-tumor tissue or cell sample to determine changes in patterns of phosphorylated S6 and IGFR expression in order to identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, including HERCEPTIN® therapy, however, no such comparison is ever made in the specification and no identification of a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy is made based on changes in patterns of phosphorylated S6 and IGFR expression, including changes of increases or decreases. Given no nexus is provided between control comparison-based changes in patterns of phosphorylated S6 and IGFR

expression and the identification of a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, one of skill in the art could not predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy based on the claimed changes, and a high quantity of experimentation would be required to determine exactly what changes in patterns compared to the claimed control would predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples for comparisons to determine changes in patterns that predictably identify a HER-2 overexpressing tumor that is likely to respond to HER-2 directed therapy, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

9. **Conclusion:** No claim is allowed. The closest prior art appears to be Lu et al (J National Cancer Institute, 2001, 93:1852-1857) and Köstler et al (J Cancer Research Clinical Oncology, 2006, 132:9-18). Lu et al teach *in vitro* Her-2 overexpressing breast cancer cell lines with inhibited or low insulin growth factor-1 receptor (IGF-IR) expression are more susceptible to trastuzumab (HERCEPTIN®) than cells with IGF-IR expression (abstract). Köstler et al teach an *in vivo* study that measured IGF-1R status in HER-2 overexpressing breast tumors and determined that response to trastuzumab therapy was independent of IGF-1R expression (abstract). Lu et al and Köstler et al do

not teach or suggest additionally measuring S6 ribosomal polypeptide phosphorylation or comparing changes in IGFR expression or S6 phosphorylation to a non-tumor sample to predict response to trastuzumab therapy.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642